

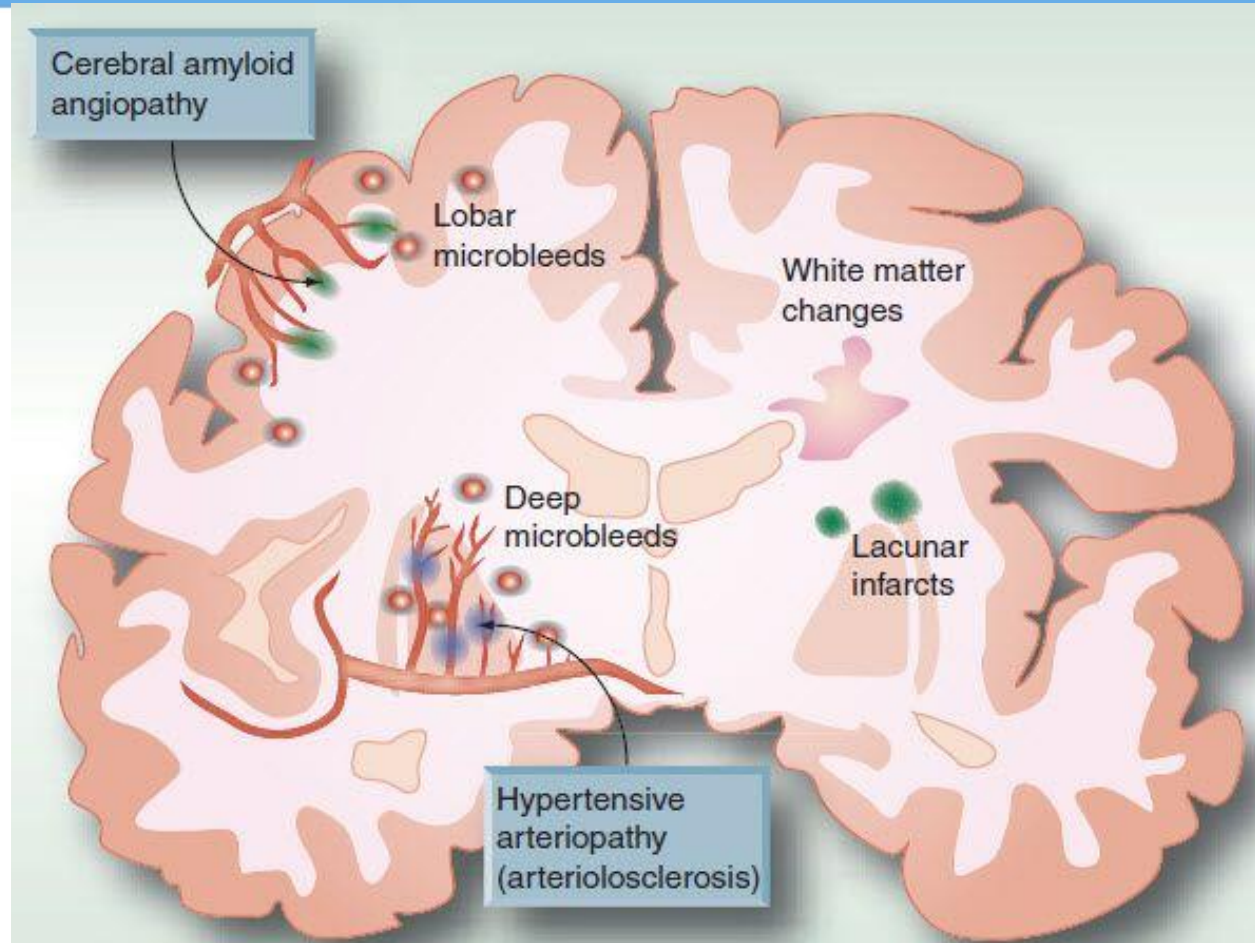
Leaky blood vessels in CADASIL

Jessica Walsh



Cerebral small vessel disease (SVD)

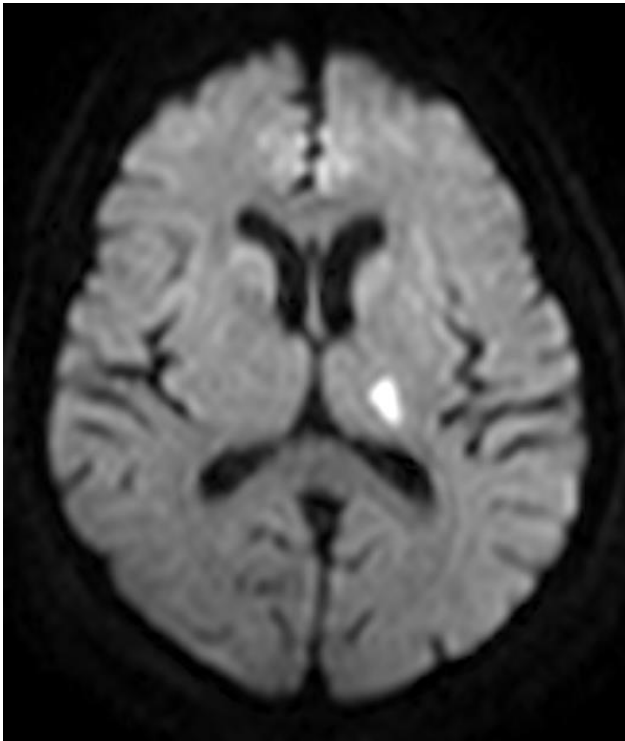
- Disease of the small deep arteries
- Symptoms include stroke, migraine and decreased cognitive function



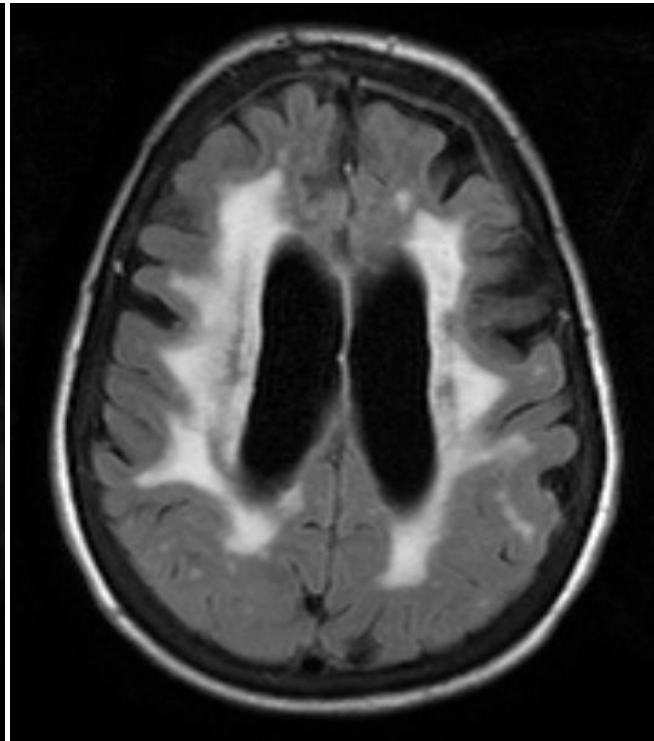
Future Neurol. © Future Science Group (2011)

Imaging SVD

MRI scans



Lacunar infarct



White matter damage

Types of SVD

Sporadic

- Commonly seen in the elderly
- Due to risk factors such as high blood pressure, smoking etc

Genetic (CADASIL)

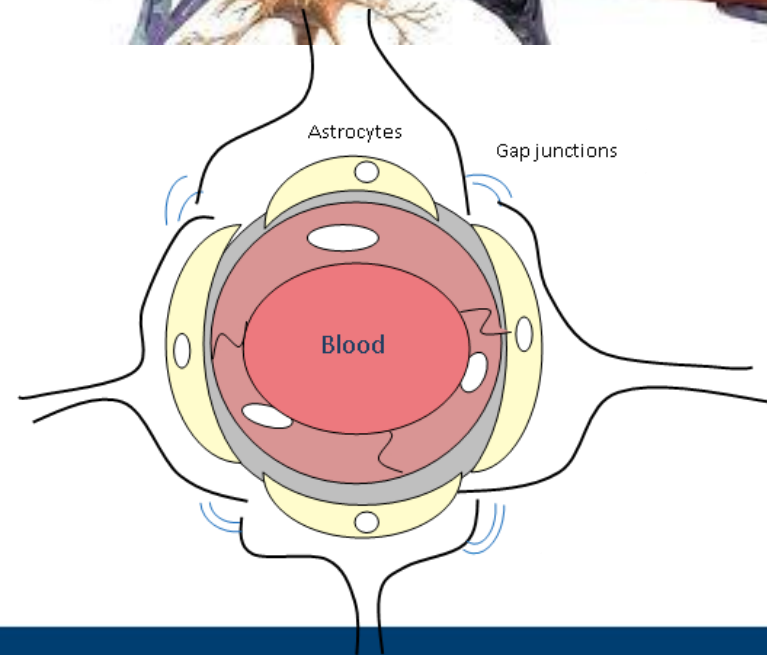
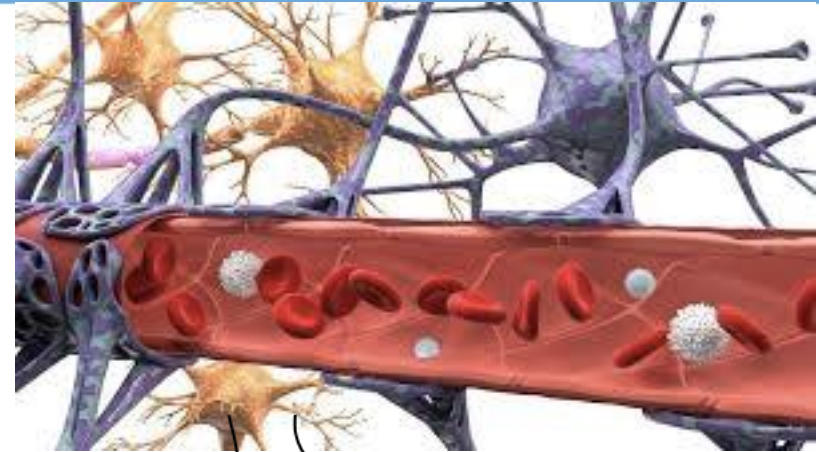
- Rare disease – prevalence of 2 in 100,000
- Due to a mutation in a gene
- Passed down through families – each child has a 50% chance

Current treatments for SVD

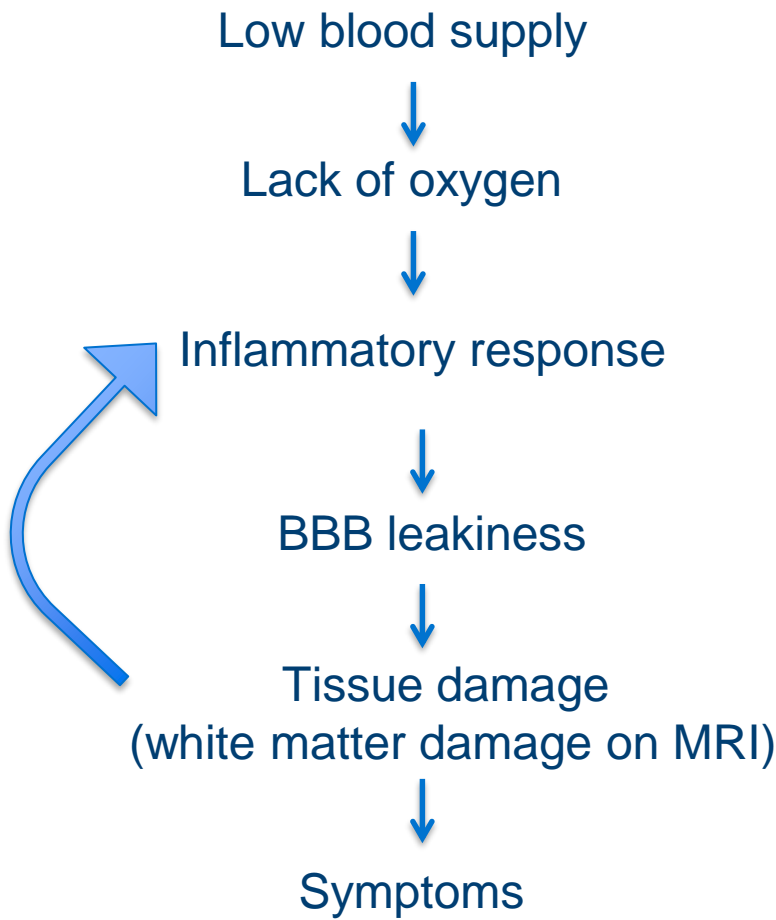
- All treatments are currently preventative or symptomatic e.g. medication to lower blood pressure
- No specific treatments that tackle the disease mechanism
- Limited by lack of understanding
- We know blood flow is reduced but this may not be the whole story

What is the blood brain barrier (BBB)?

- BBB prevents materials from the blood entering the brain
- BBB is semi-permeable
- Increased leakiness (permeability) of the BBB has been implicated in various neurological disorders including multiple sclerosis and Alzheimer's disease
- Increased leakiness would lead to increase in harmful substances into the brain

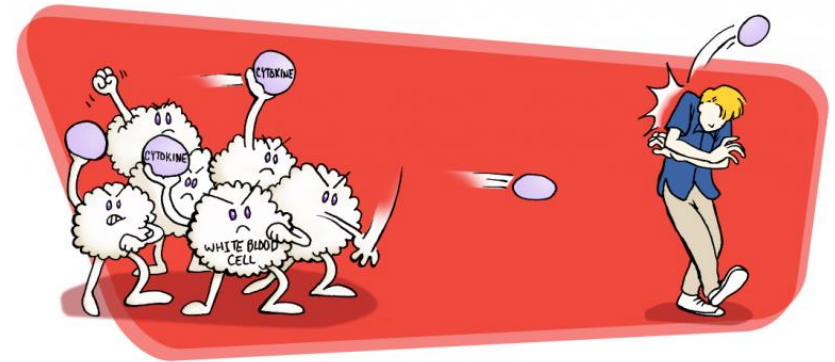


What is our hypothesis?



Hypothesis:

Inflammation leads to BBB leakiness in SVD patients, which causes damage to the brain tissue and leads to decline in cognitive function.



Rosenberg et al.,
2014 Stroke

Experimental design

Baseline

Medical history – stroke history, risk factors, medications, family history

Cognitive tests – memory, concentration etc

Imaging:

- **MRI** – clinical (lacunar infarcts and white matter lesions)
- **MRI** – BBB leakiness
- **PET** – inflammation

Blood sample – analyse for markers of BBB leakiness and inflammation

1 year

Cognitive tests – memory, concentration etc

Imaging:

- **MRI** – clinical (lacunar infarcts and white matter lesions)

Recruitment target:

Sporadic SVD = 20

CADASIL = 20

Healthy control = 20



Imaging protocol

Wolfson
Brain Imaging
Centre



PET Tracer



Gd-DOTA contrast agent



PET (80 minutes) - *Inflammation*

MRI (65 minutes) - *Leakiness*

Clinical MRI scans (to measure white matter damage and lacunar infarcts)

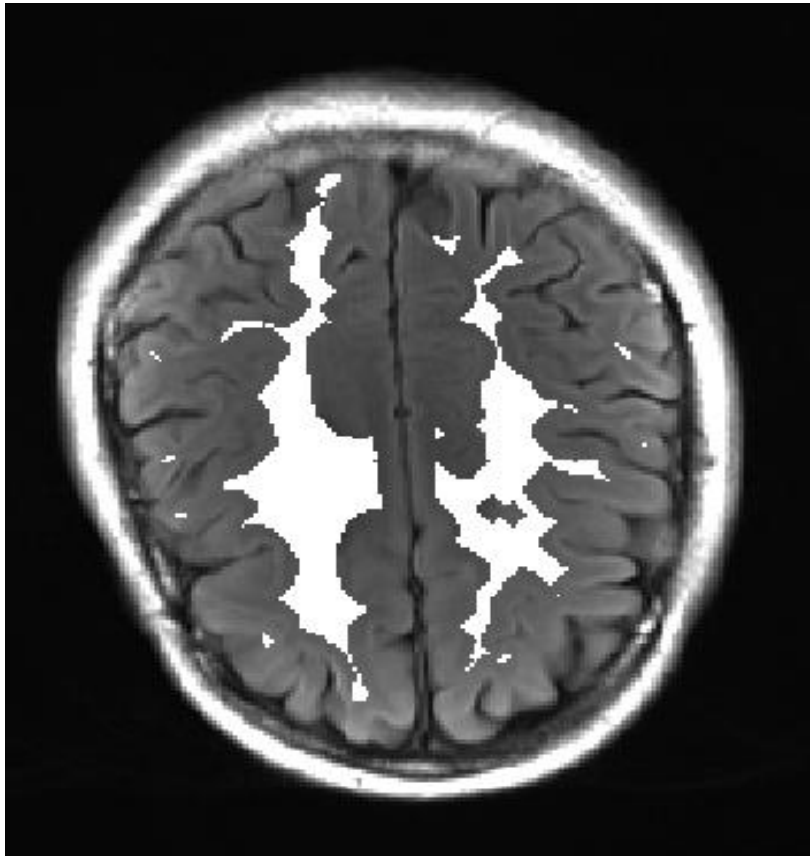
BBB leakiness scan

So far.....

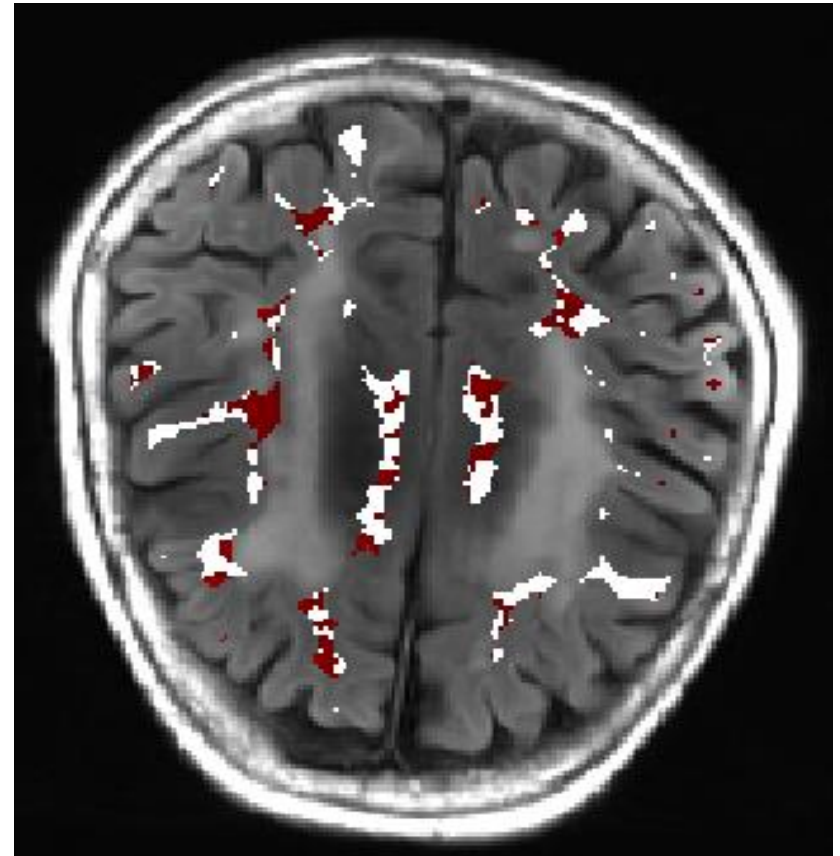
- Collected data from 39 patients:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Sporadic SVD (14)																				
CADASIL(10)																				
Healthy control (15)																				

Brain maps of leakiness



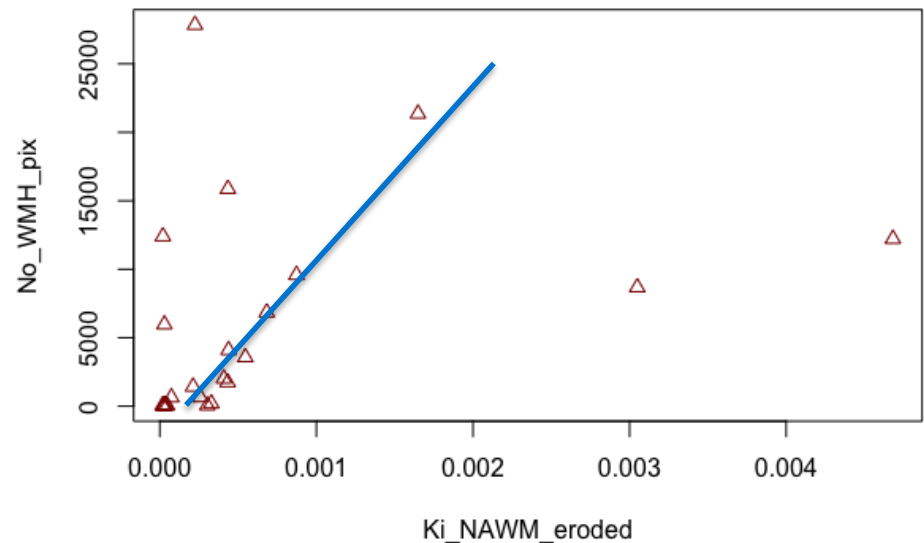
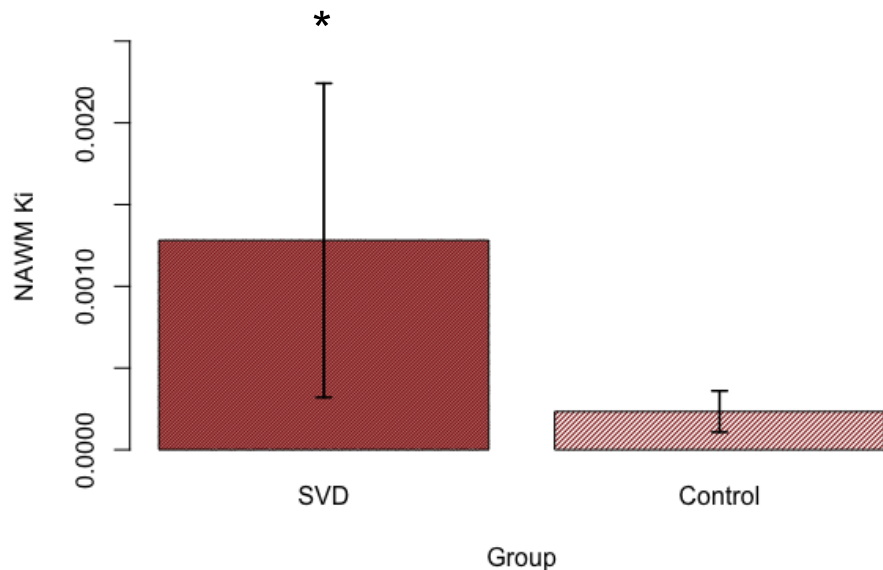
Healthy Control



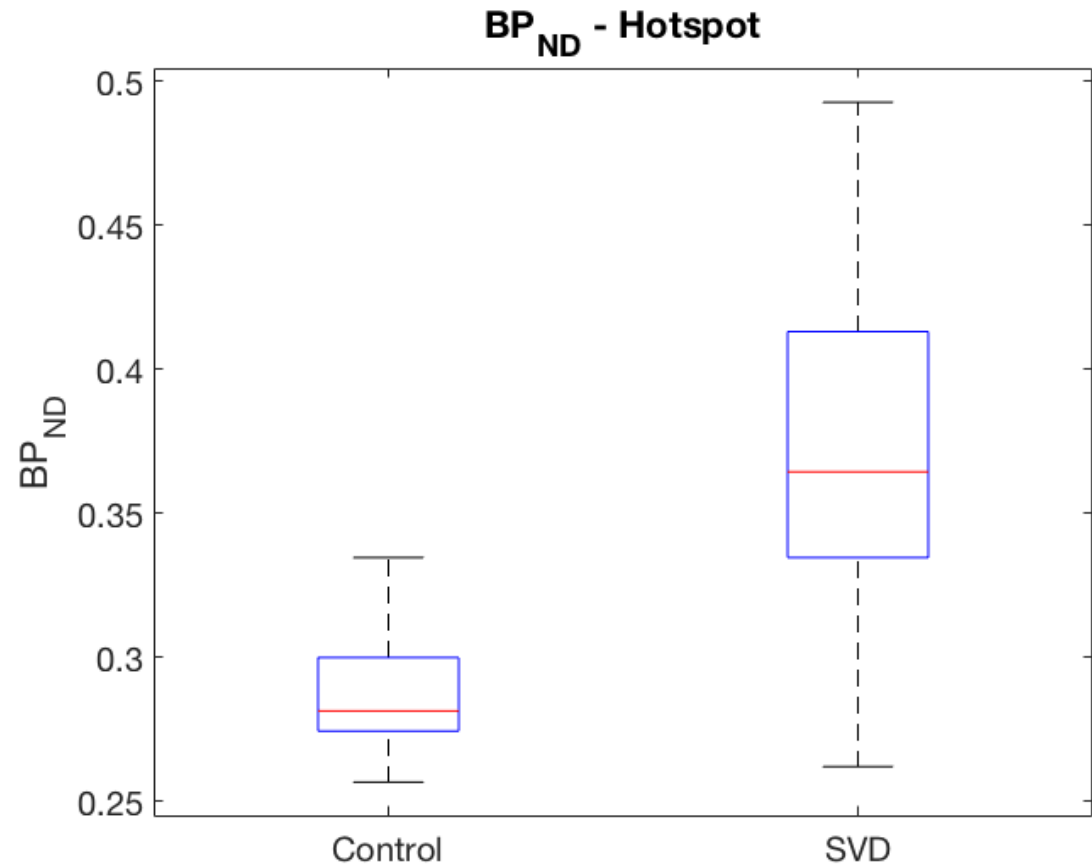
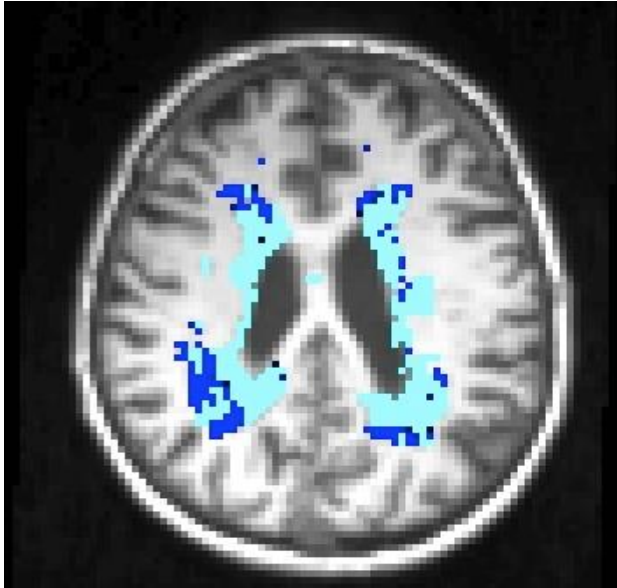
SVD Patient

Leakiness differences between groups

- Increased leakiness in SVD compared to healthy control
- Amount of leakiness correlates with the amount of damage in the brain



Inflammation is different between groups



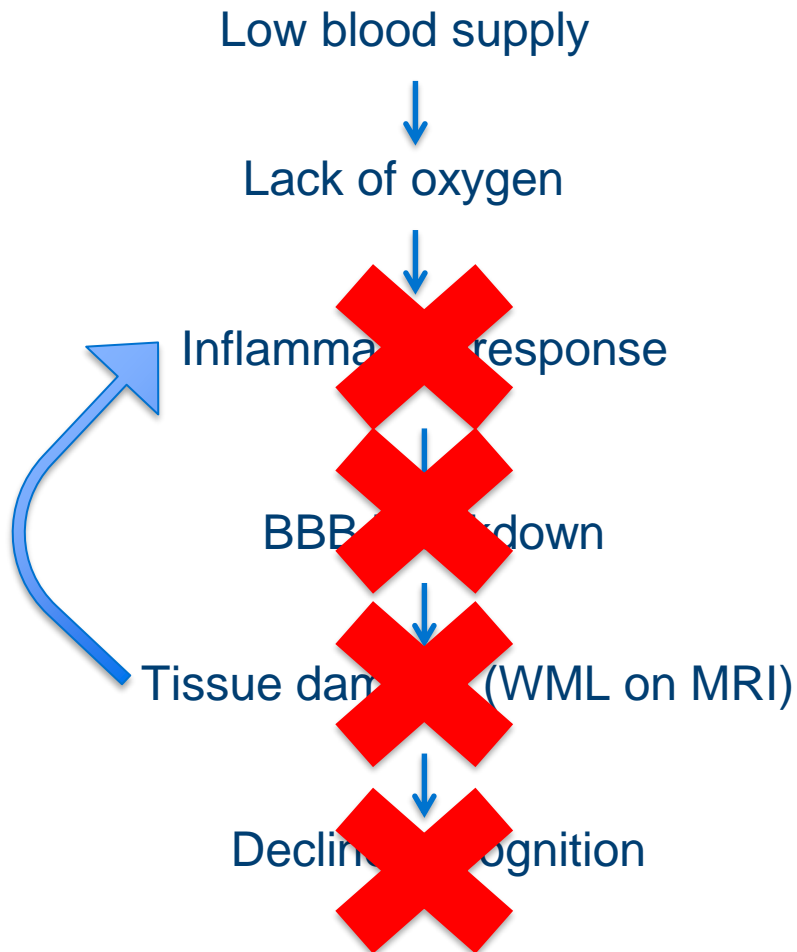
Future work

- Compare between sporadic SVD and CADASIL
- Compare with cognition data and blood samples

- Complete follow-up scans
 - See if people with increased BBB leakiness at baseline have more white matter damage 1 year later
 - See if people with increased BBB leakiness at baseline have increased cognitive decline 1 year later

- If leakiness is shown to be involved and causing damage.....

Move to drug trial



- Try a drug which blocks the inflammatory part of this pathway
- See if this reduces BBB leakiness and reduces the cognitive decline in SVD
- Could provide the first specific treatment for SVD!

Want to take part?

- We are looking for people with CADASIL as well as people without CADASIL (to act as controls) to participate in this study
- If you might be interested, fill out the research study reply slip and I will be in touch!



A huge thank you!!

- Everyone who has participated!
- Hasan Sari
- Dan Tozer
- Anna Drazyk
- Hugh Markus
- The rest of the Stroke Research Group!
- Neurosurgery labs
- WBIC



Any questions?

